

Aus der Neurologischen Universitäts-Poliklinik Basel
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The Familial Occurrence of Multiple Sclerosis

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The first acceptable case of familial multiple sclerosis (MS) was reported in 1896 by *Eichhorst*¹, in which a mother and son were afflicted. Since the turn of the century, more and more attention has been drawn to the more than just mere coincidental familial occurrence of the disease. It is interesting to note that many of the famous neurologists of the time such as *Krafft-Ebing*², *Oppenheim*³ and others did not even mention increased familial occurrence as being due to a possible endogenous etiological factor. In his article, the first of its kind, *Krafft-Ebing* vigorously endorses the exogenous, infectious etiology as existing almost beyond any doubt, and gives many examples of "traumatic" beginning of the onset of symptoms, e.g. after colds due to exposure etc., but he rejects any endogenous pre-disposing factors, such as a "*famille neuropathique*". He does admit its existence in many proven heredodegenerative diseases, such as *Friedreich's Ataxia*, etc.

No studies seriously considering familial MS appeared in the world literature during the first three decades of this century. In 1933, however, *Curtius*⁵ published his classical work on familial MS, and ever since the mere speculation of a few neurologists was turned into a relatively widely accepted fact. MS is a disease with a certain familial pre-disposing factor, as shown by the higher than just coincidental occurrence of the disease within certain families. *Curtius* compared the familial incidence of MS in 56 families living in Bonn with the occurrence in the general population of Switzerland according to *Bing* and *Reese*⁴, the ratio was at least 5 : 1, i.e., the occurrence of MS was five times more common within certain "neuropathic" families than sporadic non-familial cases. *Curtius* goes on to place the greatest emphasis on a hereditary constitutional neuropathic factor and assigns a secondary role to an additional exogenous factor (infectious or toxic). As to the nature of the endogenous factor, *Curtius* suggests the presence of "MS genes". With the addition of the exogenous factor, MS becomes manifest, without it, a general constitutional inferiority of the nervous system results. This inferiority is expressed in the increase by four times over the general population of such conditions as senile dementia, arteriosclerotic dementia, manic-depressive psychosis and other psychoses (with the exception of schizophrenia and luetic paresis).

Von Hoesslin ⁶, after reviewing 516 case histories, concluded that MS does not have an endogenous etiology, only an exogenous one. He was able to show that in one-third of the cases there was a definite trauma present before onset of the first symptoms, and that this figure would certainly have been higher had a more careful history been taken in each case. He maintains that MS is caused by an inflammatory process, partly of traumatic, partly of unknown etiology, and he supports this view by stating that the course of MS can be influenced by complete bed rest. In this case, marked improvements occasionally could be noted, whereas in the heredo-degenerative diseases, the course is unalterable. He also makes the following interesting analogy: for many years most neurologists were convinced that tabes was a hereditary disease but, overnight their theories were disproven by the discovery of the causative organism. He suggests that eventually the causative agent for MS will be found too.

More recently the general point of view taken by most authors is that both endogenous and exogenous factors are at play. These authors draw from a large source of cases from the literature plus cases from their own experience, and therefore their conclusions reflect what is generally accepted today. *Mackay* ⁷, who presents an extensive table concluded that: "MS exhibits a familial incidence more frequently than mere chance would determine. On the other hand, MS is too often non-familial for a familial constitutional factor to be its sole cause." He continues in assuming on a statistical basis that there exists a familial constitutional vulnerability to MS, which is not sufficient to cause the disease, but which along with a second non-familial exogenous factor can cause the disease to become manifest.

Pratt, Compston and McAlpine ⁸ also have a comprehensive summary of familial MS cases reported to date, and they report 33 additional families. In 310 cases the familial incidence was 20 cases, or 6.5%, which is higher than expected and statistically significant, compared with a random distribution of the disease. They conclude that "the etiological factor or factors causing disseminated sclerosis may act more readily in the presence of an inherited disposition toward the disease."

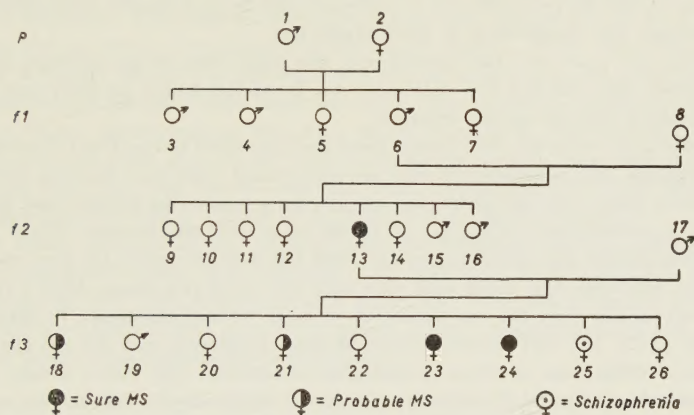
Schaltenbrand ¹¹ also arrived at the essentially identical frequency of 6.52% familial occurrence of MS in a series of 472 patients he interviewed. In a different series of 455 patients, 4.17% knew of MS cases in their immediate environment (neighbors and co-workers), blood relatives excluded. He concludes that this figure of 4.17% approaches 6.52% too closely, and that a familial disposition of MS is therefore questionable.

McAlpine, Compston and Lumsden ⁹ discuss in detail the current infectious and allergic theories, and "the hypothesis of oligodendroglial lysis". They maintain that for MS to be of an infectious etiology, the causative agent would have to have some extremely uncommon properties. A normal sedimentation rate, normal white blood count, and a lack of fever do not exclude an infectious etiology, since this is also true of some known infectious diseases of the central nervous system. In considering the allergic theory, they think it possible that in certain individuals, who have a tendency to develop hypersensitive reactions, this reaction might be localized only in the central nervous system. "The cytochemical reasons for this peculiarity are still unknown."

In the oligodendrolytic hypothesis they state that on the basis of recent studies, it is probable that the chief function of the oligodendrocyte is the daily formation and maintenance of myelin. A disease primarily affecting oligodendroglia would

result in a process selectively affecting them and the myelin sheaths only, while sparing the axons and other tissue elements. This primary disease could be due to an antigen-antibody reaction, or to an exogenous oligodendrolytic virus, or to a chemical agent, such as traces of a toxic substance having a specific affinity for the oligodendroglia, and which is released upon lysis of the damaged cells. In as far as familial occurrence is concerned, they are of the opinion that a "genetically determined predisposition", rather than a common environmental factor, or case-to-case infection is responsible, and they assume that exogenous factors may also be necessary.

The following is a family history, in which as much information as was possible to obtain from interviewing surviving relatives is presented. Detailed case histories of the mother and two daughters with MS is presented after this discussion of the family as a whole. This information was gathered in Onstmettingen (Württ.) Germany, in April 1955.



1 and 2 died of "old age"; no chronic illnesses known.

3, - 4, 5 and 7 nothing definite known.

6 died at 63 of chronic heart disease.

8 had a furuncle in cervical skin, which caused a ten year paralysis of unclear localisation. The paralysis did improve steadily up until time of death at 76, supposedly due to the furuncle (sepsis?).

9 Barbara, died at 68 of Tb.

10 Katherine, died at 68 of heart attack.

11 Juditha, died at 72 of heart attack.

12 Anna, died at 10 of childhood disease (unknown etiology).

13 Christine, had MS, died at 63 of apoplexy (case described below).

14 Rosina, died at 74 of cardiac asthma.

15 Jakob, died at 72 of "bladder disease" (Prostate?).

16 Georg, still alive, 88 years old, no chronic illnesses.

- 17 died of apoplectic stroke in his sixties, but nothing further is known about other members of his family.
- 18 * Christine B., never seriously ill, is now 62 years old. At 58 she developed a coxarthrosis. In her past history (at between 25 and 35 years), she mentioned feeling a sudden weakness in both legs, which forced her to sit down immediately for fear her legs would cave in. Once this occurred while taking a walk, the other time while rushing to catch a trolley. It took several months after each incident for her to regain the strenght in her legs. (These could have been the only manifestations of a subclinical course of MS, and a future autopsy would clear the case up). She furthermore mentioned that the house in which they lived for many years as children contained a lead pipe out of which came all their drinking water. Her mother (No. 13) was 26 years old at the time she moved into this house. All except the first two children were born by the mother (No. 13) in that house, and they all grew up there. The family physician often warned them about the dangers of the lead pipe. Christine B., when moved out of the house after her marriage, has two children and six grandchildren, all of whom are in good health.
- 19 Emmanuel, 60 years old, not interviewed, but in good health, according to his siblings. One daughter is in good health too.
- 20 Anna, 58 years old, not interviewed, but according to her siblings, she has written that she can not walk well, nor move her hands properly any more. Relatives believe she has arthritis.
- 21 Bertha, 57 years old. Was interviewed and examined in the Basel Neurological Policlinic. She is unmarried. She has had several childhood diseases, including scarlet fever. She has undergone surgery for a wandering kidney, and has had an appendectomy. At the age of 33, she once suddenly became "tired" in the sacral region, and noticed that she could not properly move her legs, and that they felt weak. She could walk only with the aid of two canes. After a thirteen week salinic cure, she was again able to walk without the canes. In the following years, she had no recurrences of these symptoms, nor did she ever have visual difficulties or other neurological symptoms. She had a steady severe headache (migraine?) for many years, for which she had found no remedy. Recently she had influenza (diagnosed by her family physician), and since then she has noticed an increased weakness in her legs again. She complains of nightly cramps she gets upon retiring, and says that they usually start in her right leg, and then move over to her left leg. She says that these cramps force her toes inward, and a flexion of her knees. When this occurs, she can neither stand up, nor straighten her knees out, due to severe pain. She also mentioned having had a rash on her legs and waist for the past few months.

Neurological examination of April 1954 showed essentially: no temporal pallor of the discs, horizontal nystagmus (dissociated) towards the left, negative pyramidal signs (i.e. negative Babinski, Gordon and Oppenheim), but abdominal reflexes were decreased. Patellar reflexes slightly exaggerated, Achilles tendon reflexes both absent. No sensory disturbances were apparent, and there were no signs of motor disturbances. Psychologically depressive type. In this

* Questioned only at home, since she refused examination in the Neurological Policlinic. She was interviewed in April 1955.

case, on the basis of the history, one could also contemplate another possible subclinical form of MS. Especially noted should be the onset of her first complaints at the age of 33.

- 22 Minna, died at the age of ten of diphtheria. Was twin of Emma (No. 23).
- 23 Emma, died at the age of 51 of MS (described below).
- 24 Lina, 51 years old, has MS (described below).
- 25 Martha, died at 39 years of age of teratoma adultum. At the age of twenty she developed acute schizophrenia, followed by a catatonic stupor, for which she was occasionally institutionalized. She died during the operation of the teratoma. (From case history of Univ. Surgical Clinic, Basel.)
- 26 Marie, according to siblings, she was never seriously ill, and is suffering from arthritis for some time now.

Case report of the mother and two daughters suffering from MS.

Christine K. B. (f 2 No. 13), born 1868.

Nothing about childhood diseases could be ascertained. As mentioned above, at the age of twenty-six, she moved into the house in which the drinking water came out of a lead pipe. When she was thirty two years of age, her son fell out of a window, causing her to have a considerable psychological trauma. From that day on, she started to "drag" her left leg, and was never able to move it properly again. At forty-one years of age, she gave birth to her last child, after which she could not walk any more at all, and could stand up only with the aid of supports. Her upper extremities became affected when she was fifty-one years old; it became impossible for her to move her right hand and her left arm and hand. No excretory or visual difficulties were reported. She died at the age of sixty-three of an apoplectic stroke.

The above information was gathered from her surviving children and relatives, who furthermore stated that Christine was diagnosed as MS clinically by two family physicians. Their records or own statements were not accessible. Nor was Christine ever hospitalized so that a record of her symptomatology and results of more exact examinations are not available.

Emma B. (f 3 No. 23), daughter of Christine K. B., was never married. Never ill, except with childhood diseases. Was always mentally "slow". At the age of thirty, she began to have difficulties in walking, since her legs became progressively stiffer; they were contracted at the knees and hips and adducted. She also became progressively increasingly dement, so that she had to be institutionalized. She was periodically examined by Prof. Georgi of the Basel Neurological Clinic, who noticed her increasing paralysis and dementia. At his final examination, he wrote "spastic tetraplegia with intention tremor, ataxia and euphoric dementia", and his diagnosis was MS.

A "modified Quick Test" (i.e. hippuric acid excretion, which has been produced as a result of p. o. doses of sodium benzoate, first without and then with the addition of glycin) showed a great increase of the previously diminished excretion in hippuric acid after addition of glycin in this case, and so liver damage can be assumed.

She died at the age of fifty-one. The autopsy report of the Basel Pathological Institute, read: "Severe atrophy of the brain (1050 grams) with multiple irregularly distributed foci, especially around the ventricles, in the hippocampus, in areas adjacent to the frontal and occipital cortices, in the pons, and medulla oblongata.

Severe affection and marked distribution of sclerotic foci throughout the spinal medulla. Hydrocephalus internus, and decubital ulcers of the trochanter regions associated with contractures of the lower extremities.

Diagnosis: Multiple Sclerosis, mainly localized in the brain (10)."

Lina B. (f 3 No. 24), daughter of Christine K. B., was never married. Had only usual childhood sicknesses. At the age of twenty-four, she once suddenly became very dizzy, her eyes "flickered", she fell to the ground and vomited a greenish yellow fluid. She never lost consciousness, but due to her vertigo, was unable to get up, and so had to be carried to bed. Thereafter, she noticed that whenever she fixed her eyes on an object to her left, she became dizzy. This lasted about four weeks, after which time she got out of bed and her visual disturbances ceased. She took up her work as a clerk again, and had no complaints until six years later, when she was thirty years old. At that time she noticed that she often banged her left leg into things. She also noticed that her sensation around her left knee was markedly reduced. When walking, she would tire easily and sometimes she had the feeling that her left leg was longer than her right leg. Her left leg became worse steadily, until she could hardly move it any longer. Next she noticed that she could not move her left hand properly and complained of a velvety feeling in it. At the age of forty, she noticed having co-ordination difficulties with her right leg, and could not move it properly any longer either. She managed to walk with the aid of canes, until at the age of 47, she once suddenly fell down, and was unable to get up again, even with assistance. The contractures of both legs became much more pronounced from that day on. Her left leg had fibrillar twitchings for about eleven years. She had pains only in her right leg, between the knee and ankle. Six weeks prior to interview, her symptoms suddenly became more pronounced. She is very euphoric, with only little sign of dementia.

The most recent neurological examination showed the following pathological conditions: Temporal pallor of both discs. On her left arm, the following reflexes were lacking - radial periost, biceps and triceps; her interosseous muscles of the left hand were markedly atrophic. Abdominal reflexes missing on the right side, reduced on the left.

Both legs in extremely contracted (flexed and adducted) position. No patellar or ankle reflexes were producible. Babinski, Gordon and Oppenheim strongly positive bilaterally. No voluntary movements possible. No excretory difficulties were present. She had a pathological value of the modified Quick Test (i.e. a reduction in the availability of endogenous glycine for detoxification). Considering the chronic process, with occasional exacerbations, and the symptoms mentioned above, there can be little doubt as to the diagnosis of MS. The neurological examination was done in April 1955 in the Altersheim of the Bürgerspital, Basel.

Discussion

As is evident from the literature, a familial occurrence of MS can occasionally be observed, more frequently than mere chance or coincidence would indicate. It is generally believed that some unknown environmental exogenous factor (of traumatic, infectious, allergic or metabolic nature) must be present. Furthermore, mention

is made of other exogenous factors, such as a chronic intoxication, or poor dietary or sanitary conditions leading to a generalized decrease of body resistance to the disease in the MS family. An exogenous factor, acting on only one member of a family, could explain sporadic cases, when acting on the whole family, it could explain familial occurrence.

On the other hand, many authors believe that in addition to the exogenous etiologic factor, there is another factor present which is responsible for the familial occurrence. This could be a genetic constitutional (endogenous) weakness or vulnerability of the central nervous system. Much speculation about this genetic factor has been expressed in the literature, but as yet there is no accord as to its character or modality. It is improbable that it is dominantly inherited, because of the scarcity of MS occurrence amongst siblings (only 2 out of nine in our observation). Furthermore, it is interesting to note that not one example of a skipping of a generation of MS has ever been reported in the literature. This makes recessive or sex linked inheritance unlikely.

In the family here reported (P, f 1, f 2 and f 3), there is no evidence of an endogenous genetic predisposing factor. *Curtius* considered such evidence being expressed by the manifestation of other neurological diseases or psychoses in families with „weakened” central nervous system. This (i.e. such diseases in previous generations) were not found in our family, since only the members of the f 3 generation and their mother were affected. These all grew up or lived in the same immediate environment, and so we believe that a common exogenous environmental factor deserves closer consideration. There has been one possible exogenous factor mentioned, which, in accordance with the literature, could have played a role. This was the fact that the drinking water of the whole family came out of a lead pipe (specifically mentioned by Christine K. B. f 3). The mother lived in this house for six years before her first symptoms appeared. Subsequently, two of her children got MS, another probably has it (No. 21), a fourth is suspicious (No. 18), and another was afflicted with schizophrenia (No. 25).

Lead is a heavy metal poison which interferes with enzymatic mechanisms. „Chronic lead poisoning may also occur from drinking water carried in lead pipes. – Other findings frequently present are degeneration of anterior horn cells¹²”. Mental disturbances may also occur. The chronic plumbism which may be present in our cases

could be interpreted as being a *predisposing* environmental factor, acting in conjunction with yet another exogenous *etiologic* factor. Few authors deny the existence of an *environmental* factor, which may be predisposing or etiologic.

Both pro and con views as to the role of lead in MS are represented in the literature. *Campbell*¹³ et al. tried to prove that an increased lead content in the soil in certain regions favours the incidence of MS in the population. On the other hand, *Butler*¹⁴ made an extensive study of lead urinary excretion of clinically certain MS cases, and compared his results with those gathered from patients with other chronic neurological diseases and found no difference. He concluded that „the studies reported do not support the view that lead plays a part in the etiology of disseminated sclerosis and certain other chronic diseases of the nervous system”.

Finally, *de Morsier*¹⁵ reports a case of two brothers, both of whom got MS at the age of 42; both of whom were housepainters. He was able to find an abnormally increased amount of lead in a tooth of one of them. He believes that MS might be an allergic reaction, in which the lead plays a predisposing rather than etiologic role, via involvement in an antigen-antibody reaction.

It should also be mentioned that a frequent finding in MS patients reported by *Georgi* and *Beuthien*¹⁶ is the presence of pathological values of liver function tests. Specifically they demonstrated a decreased production of hippuric acid by means of a modified Quick Test. This was not the only liver function test to have pathological values. In the case of our two sisters, the production of hippuric acid* was markedly diminished. As mentioned above, the method used was the detoxification of sodium benzoate before and after addition of exogenous glycine. The mother was not tested.

In view of the complex enzymatic functions of the liver, it would not be unlikely that some hepato-toxic agent (predisposing or etiologic) is involved in the pathogenesis.

On the basis of this discussion, we conclude that the role of chronic lead intoxication should continue to receive attention as a possible exogenous co-factor in the pathogenesis of MS. Taking into account the extensive research *Georgi* has done on the detoxification damage in the liver plus the possibility that lead may disturb some of the complex enzymatic mechanisms of the liver, we believe that these two factors are worthy of continued further investigation.

* Without additional glycine.

I would like to express my deep gratitude to Prof. *F. Georgi*, chief of the Basel Neurological Policlinic, for his kind inspiration and guidance of this work. I would also like to thank Dr. *D. Jordan* for her many helpful suggestions and assistance in the completion of this paper, furthermore Dr. *A. L. Vischer* (former head of the Altersheim of the Bürgerspital, Basel), for permitting me access to his case histories, which I used, in part, herein.

Summary

The case of a mother and two of her daughters all having MS has been presented, with particular reference to a discussion of exogenous and endogenous factors, which may be either predisposing or etiologic. A review of the literature concerning the familial occurrence of MS has shown the importance various authors ascribe to the possible role of these factors.

The distinction between predisposing and etiologic factors has been discussed and reference has been made to the existence of hepatic damage in two of our cases, and its frequency in MS. Chronic lead poisoning has been mentioned as perhaps being of some importance in the pathogenesis of MS.

Zusammenfassung

Ein Fall von familiärem Vorkommen von multipler Sklerose (MS), in dem die Mutter und zwei ihrer Töchter an MS erkrankten, wird veröffentlicht. Die Rolle exogener und endogener Faktoren, die entweder ätiologisch oder prädisponierend sein können, wird besprochen. Eine Literaturübersicht zeigt die Bedeutung, welche die meisten Autoren diesen Faktoren zukommen lassen.

In der Diskussion wird die Tatsache hervorgehoben, daß bei zwei von unseren Probanden eine Leberschädigung vorhanden war, wie sie auch sonst bei MS oft gefunden wird. Chronische Bleivergiftung wurde als eventuell auch wesentlicher ätiologischer Faktor in der Pathogenese der MS diskutiert.

Résumé

L'auteur présente un cas familial de sclérose en plaques (M.S.), la mère et deux de ses filles étant atteintes. Il expose le rôle des facteurs exogènes et endogènes qui peuvent être soit étiologiques soit prédisposants. Une revue de la littérature montre quelle importance la plupart des auteurs ont attribué à ces facteurs. Il ressort de la discussion du cas que chez deux des patientes décrites existait une atteinte du foie, dont la fréquence semble d'ailleurs avoir été prouvée

dans la MS. Un autre facteur pouvant éventuellement jouer un rôle étiologique dans la pathogénèse de la MS pourrait être l'intoxication chronique au plomb.

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